51. The method of any one of claims 1 and 40 through 44, wherein the biological conduit is surgically exposed and the agent is delivered into the lumen or is applied to the external surface of the biological conduit *in vivo*.

52. The method of any one of claims 1 and 40 through 44, wherein a biological conduit is surgically removed and the agent is delivered to the lumenal surface and/or to the external surface of the conduit *in vitro*.

53. The method of any one of claims 1 and 40 through 44 wherein the agent causes the production and/or release of endogenous enzymes that solubilize and/or degrade the central amorphous material of elastin and/or the microfibrillar component of elastin within the wall of the biological conduit.

54. The method of any one of claims 1 and 40 through 44 wherein the agent causes the production and/or release of endogenous enzymes that solubilize and/or degrade collagen fibers within the wall of the biological conduit.

55. The method of any one of claims 1 and 40 through 44, wherein after administration of the agent, a time period is permitted to lapse sufficient for the administered therapeutic agent to permeate through the walls of the biological conduit.

REMARKS

Claims 1-12 are pending in the subject application. Claims 1 and 5-12 have been amended for clarification purposes. Claims 40-55 have been added. Support for the amendment to claims 1 and 5-12 and for added claims 40-55 is found throughout the Specification, as filed, and no new matter is presented by the amendment (e.g. see page 9, lines 2-11; page 16, lines 10-22; page 8, lines 18-24; page 6, lines 19-28; page 13 line 12 - page 14 line 12) Further, Applicant has included the terminology that the agent is capable of "solubilizing and/or degrading the central amorphous material of elastin and/or the microfibrillar component of elastin." Applicant respectfully submits that the

application as filed discloses that the therapeutic agent is capable of degrading the extracellular matrix of the obstructing tissue, particularly elastin (see, e.g. page 6, lines 2-5; page 10, lines 7-9; page 10, lines 23-24). Elastin fibers are composed of the central amorphous material of elastin and the microfibrillar component of elastin. Applicant respectfully submits that degradation and/or solubilization of elastin fibers would necessarily involve degradation and/or solubilization of the central amorphous material of elastin and the microfibrillar component of elastin, and, thus, this terminology does not introduce new matter. MPEP 608.04(a), 2163.07(a).

Favorable reconsideration in light of the amendments and remarks which follows respectfully requested.

1. 35 U.S.C. §112 Rejections

Claims 2-12 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention.

In particular, the Office states "The phrase 'otherwise degrade' in claims 2-4 makes those claims indefinite."

Claims 2-4 have been cancelled, without prejudice. Thus, rejection of these claims is moot.

The Office further states that applicant should replace the term "collogen" with "collagen." Applicants have corrected this typographical error as suggested.

The Office further states "The phrase 'standard *in virto* tissue digestion assay' in claims 6-7 renders those claims indefinite because of the word 'standard'. This term does not clearly define a 'standard assay'."

Applicants respectfully submit that definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. See MPEP §2173.02.

Applicant respectfully submits that a standard *in vitro* tissue digestion assay is clearly defined in the application disclosure as follows:

> More particularly, a candidate therapeutic compound can be identified in the following *in vitro* assay that includes steps 1) and 2):
>
> 1) contacting comparable mammalian tissue samples with i) a candidate therapeutic agent and ii) a control (i.e. vehicle carrier without added candidate agent), suitably with a 0.1 mg of the candidate agent contacted to 0.5 ml of the tissue sample; and
>
> 2) detecting digestion of the tissue sample by the candidate agent relative to the control. Digestion can be suitably assessed e.g. by microscopic analysis. Tissue digestion is suitably carried out in a water bath at 37°C. Fresh pig tendon is suitably employed as a tissue sample. The tissue sample can be excised, trimmed, washed blotted dry and weighed, and individual tendon pieces suspended in 3.58 mg/ml HEPES buffer at neutral pH. See Example 1 which follows for a detailed discussion of this protocol. Such an *in vitro* protocol that contains steps 1) and 2) is referred to herein as a "standard *in vitro* tissue digestion assay" or other similar phrase.

Page 11, lines 1-16.

It is respectfully submitted than claims 5-12 comply with 35 U.S.C. §112. Reconsideration and withdrawal of the rejection is respectfully requested.

2. 35 U.S.C. §102 Rejections

Claims 1-8 have been rejected under 35 U.S.C. §102(e) as being anticipated by Gokeen et al. (U.S. Patent 5,116,615). The Office states:

> Gokeen et al., disclose a method to relieve obstructive symptoms resulting from benign prostatic hypertrophy by transurethrally injecting a therapeutically effective dosage of a composition comprising hydrolyzing

enzymes (Abstract) collagenase and elastase among other proteolytic and non-proteolytic enzymes (Column 2, Lines 30-68). In the said method, the said obstruction is relieved because of the dissolution of the hypertrophied prostatic tissue that causes rectal or urinary (i.e., a biological conduit) obstruction (Abstract, Column 3, Lines 45-46). Gokeen et al., further disclose an in-vitro assay (Column 42, Line 64 to Column 43, Line 7), wherein giuinea pig prostate tissue treated with the said composition comprising enzyme or enzyme mixture is completely digested (up to 100% digestive activity).

Applicants respectfully traverse this rejection.

The present method describes the treatment of an obstructed biological conduit or a biological conduit susceptible to obstruction. According to the present method, an agent is delivered to the wall of the conduit. The agent is one that is capable of solubilizing and/or degrading the elastin matrix of the wall of the biological conduit. In particular, administration of the agent causes solubilization and/or degradation of the central amorphous material of the elastin fiber and/or the microfibrillar component of the elastin fiber, which thereby reduces the elasticity of the conduit wall. The loss of elastin then leads to elongation of the wall of the conduit and reorganization of the collagen matrix which results in enlargement of the lumen diameter. During and after treatment, the tissue remains grossly intact and the cells remain viable.

The Gokeen reference, on the other hand, describes the treatment of benign prostate hypertrophy (BPH). BPH is a nodular, irregular enlargement of the prostate gland. The prostate gland surrounds the urethra, the canal through which urine passes out of the body. Enlargement and swelling of the prostate gland, as with BPH, can result in a blockage of flow through the urethra. According to Gokeen, an agent is delivered to the prostate gland, not the conduit, which would be the urethra. Further, the agent causes the breakdown of tissue integrity and the bulk removal of collagen, elastin and cells in the prostate. Still further, administration of the agent to the relatively thick prostate gland, is very different than administration of an agent to the thin wall of a biological conduit. An

agent designed to modify the wall of a biological conduit must not lead to breakdown of tissue integrity since this breakdown could lead to the formation of a hole through the full thickness of the biological conduit wall, which would be very undesirable.

Thus, the present invention teaches a method wherein an agent is administered to a biological conduit so as to release the constrictive radial force exerted by elastin fibers which act to limit the diameter of the conduit. In other words, according to the present invention, the agent degrades the central amorphous material of the elastin fiber and/or the microfibrillar component of the elastin fiber, which reduces the elasticity of the conduit, thereby allowing for elongation of the wall of the conduit and enlargement of conduit diameter. This agent leaves the integrity of the tissue intact and the cells of the tissues remain viable. The Gokeen reference, on the other hand, describes the intentional disruption of tissue integrity and the complete removal of tissue (including cells, collagen, and elastin) in a gland that surrounds a biological conduit. The agent described by the Gokeen reference is elastase and a non-specific protease, wherein the non-specific protease is the main component. This agent is not controllable and will dissolve tissues completely.

As provided in MPEP-2131, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Or stated another way, "The identical invention must be shown in as complete detail as is contained in the ... claims. *Richardson v Suziki Motor Co.*, 868 F.2d 1226, 9 USPQ 2d. 1913, 1920 (Fed. Cir. 1989). Although identify of terminology is not required, the elements must be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

It is clear from the foregoing remarks that the above-identified claims are not anticipated by the Gokeen reference.

2. 35 U.S.C. §103 Rejections

Claims 1-12 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Gokeen et al. (U.S. Patent 5,116,615) in view of Kunz et al. (U.S. Patent 6,074,659).

Applicants respectfully traverse this rejection.

As set out above, the Gokeen reference fails to describe or otherwise suggest the administration of an agent to a biological conduit. Further, the Goken reference fails to describe the administration of an agent to solubilize and/or degrade the central amorphous material of the elastin fiber and/or the microfibrillar component of the elastin fiber in the biological conduit wall. Rather, the Gokeen reference describes administration of an agent to a gland that surrounds a biological conduit. Further the agent described by Gokeen completely and non-specifically disrupts the integrity of the tissue and removes collagen, elastin and cells.

Likewise, the Kunz reference fails to describe or otherwise suggest the administration of an agent to solubilize and/or degrade the central amorphous material of the elastin fiber and/or the microfibrillar component of the elastin fiber in the biological conduit wall, thereby facilitating elongation of the wall of the conduit and enlargement of conduit diameter.

Accordingly, claims 1 and 40-44 are patentable over Gokeen in view of Kunz. Claims 2-4 have been cancelled, without prejudice and, thus, rejection of these claims is moot. Claims 5-12 and 46-55 depend from claims 1 and 40-44 and, likewise are patentable over Gokeen in view of Kunz.

CONCLUSION

Reconsideration and allowance of claims 1, 5-12 and 40-56 is respectfully requested in view of the foregoing discussion. This case is believed to be in condition for

immediate allowance. Applicant respectfully requests early consideration and allowance of the subject application.

If for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105**.

Should the Examiner wish to discuss any of the amendments and/or remarks made herein, the undersigned attorney would appreciate the opportunity to do so.

Respectfully submitted,

Date: Dec. 17, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE IN CLAIMS

Please note that additions to the claims are shown underlined and deletions are shown in brackets.

1. A method for treating an obstructed biological conduit or a conduit susceptible to obstruction, comprising administering to the wall of the conduit an agent which results in the [that can] solubilization and/or degradation[e] of the extracellular matrix fibers within the wall of the biological conduit leading to enlargement of the lumen diameter.

5. The method of [any one of] claim[s] 1 [through 4] wherein the agent comprises an enzyme or a mixture of enzymes that can solubilize and/or degrade elastin, including the central amorphous component and the microfibrillar component.

6. The method of [any one of] claim[s] 1 or [through] 5 wherein in a standard *in vitro* [tissue digestion] assay, the agent exhibits at least [about] 10 percent greater [digestion] activity against either the amorphous material of elastin or the microfibrillar component of elastin, relative to a control.

7. The method of [any one of] claim[s] 1 or [through] 5 wherein in a standard *in vitro* [tissue digestion] assay, the agent exhibits at least [about] 50 percent greater [digestion] activity against either the amorphous material of elastin or the microfibrillar component of elastin, relative to a control.

8. The method of [any one of] claim[s] 1 [through 7] wherein the agent can solubilize and/or degrade the central amorphous component of elastin and/or the microfibrillar component of elastin.

9. The method of [any one of] claim[s] 1 [through 8] wherein the agent is administered by a catheter.

10. The method of [any one of] claim[s] 1 [through 9] wherein the obstruction of the biological conduit is a stenosis, stricture or lesion.

11. The method of [any one of] claim[s] 1 [through 10] wherein the biological [conducit] conduit is an artery, vein, [ureteter] ureter, bronchi, bile duct, or pancreatic duct.

12. The method of [any one of] claim[s] 1 [through 11] wherein the agent is administered to a mammal having an obstructed biological [conducit] conduit, or susceptible to an obstructed biological conduit.

Kindly add the following new claims:

40. A method for treating an obstructed biological conduit or a conduit susceptible to obstruction, comprising administering to the wall of the biological conduit an agent that can solubilize, and/or degrade a portion of the extracellular matrix of the wall of the biological conduit.

41. A method for treating an obstructed biological conduit or conduit susceptible to obstruction, comprising administering to the wall of the biological conduit an agent that can solubilize and/or degrade the central amorphous material of elastin and/or the microfibrillar component of the elastin in the wall of the biological conduit, leading to enlargement of the lumen diameter of the biological conduit.

42. A method for treating an obstructed biological conduit or conduit susceptible to obstruction comprising:

administering to the wall of the biological conduit an agent; and

allowing the agent to solubilize and/or degrade a portion of the extracellular matrix of the biological conduit wall, leading to an enlargement of the lumen diameter of the biological conduit.

43. A method for treating an obstructed biological conduit or conduit susceptible to obstruction comprising:

administering to the wall of the biological conduit an agent;

allowing the agent to solubilize and/or degrade the central amorphous material of elastin and/or the microfibrillar component of the elastin in wall of the biological conduit, leading to an enlargement of the lumen diameter of the biological conduit.

44. A method for treating a obstructed biological conduit or conduit susceptible to obstruction comprising:

reducing the elasticity of the conduit wall by administering an agent to the biological conduit, whereby the agent is capable of solubilizing and/or degrading the central amorphous material of elastin and/or the microfibrillar component of elastin within the wall of the biological conduit.

45. The method of any one of claims 1 and 40 through 44, wherein administration of the agent comprises localizing a delivery apparatus in close proximity to the segment of the biological conduit to be treated.

46. The method of claim 45, wherein the method further comprises the step of inserting a portion of the delivery apparatus into the wall of the biological conduit.

47. The method of any one of claims 1 and 40 through 44 further comprising the step of pressurizing the lumen of the biological conduit while an agent, which degrades extracellular matrix fibers in the wall, is delivered to the pressurized segment of the biological conduit.

48. The method of claim 47, wherein the lumen of the biological conduit is pressurized by mechanical action.

49. The method of claim 47, wherein the lumen of the biological conduit is pressurized with a balloon catheter.

50. The method of claim 47, wherein the agent is administered and the pressurizing is performed by the same device.

51. The method of any one of claims 1 and 40 through 44, wherein the biological conduit is surgically exposed and the agent is delivered into the lumen or is applied to the external surface of the biological conduit *in vivo*.

52. The method of any one of claims 1 and 40 through 44, wherein a biological conduit is surgically removed and the agent is delivered to the lumenal surface and/or to the external surface of the conduit *in vitro*.

53. The method of any one of claims 1 and 40 through 44, wherein an artery is obstructed by atherosclerosis.

54. The method of any one of claims 1 and 40 through 44 wherein the agent causes the production and/or release of endogenous enzymes that solubilize and/or degrade the central amorphous material of elastin and/or the microfibrillar component of elastin within the wall of the biological conduit.

55. The method of any one of claims 1 and 40 through 44 wherein the agent causes the production and/or release of endogenous enzymes that solubilize and/or degrade collagen fibers within the wall of the biological conduit.

56. The method of any one of claims 1 and 40 through 44, wherein after administration of the agent, a time period is permitted to lapse sufficient for the administered therapeutic agent to permeate through the walls of the biological conduit.